Correlation of HbA1c with Mortality and severity in Acute Coronary Syndrome

T. N. Dubey[1], Kaustubh Mundada[2], A Arya[3]

ABSTRACT

Introduction: Coronary Artery Disease (CAD) has emerged as the single most important cause of death worldwide and as well as in India. Diabetes Mellitus (DM) is a major risk factor for CAD and there appears to be a **graded** rise in cardiovascular risk with increasing degrees of glucose intolerance well below the definition of overt diabetes. The aim of the study was to define the relationship between HbA1c levels with mortality, morbidity and severity in patients with Acute Coronary Syndrome (ACS).

Material and Methods: This was an observational prospective study. The sample size was 110 patients with ACS. Detailed history, examination and investigations were done as per preformed proforma. ECG, CPK-MB, echocardiography was done in all patients and coronary angiography (CAG) was done in half of the patients.

Results: The mean age was 58.17 ± 9.87. Out of 110 patients, 64 (57.2%) were non-diabetic, 27 (24.5%) were diabetic and 20 (18.2%) had impaired glucose tolerance 46 patients (41.8% of patients) had hypertension. The most common complications were left ventricular dysfunction (LVD) and Heart Failure (HF) and this were significantly more present in diabetics compared to nondiabetics (p value 0.009). The mean HbA1c level was higher in patients with complications (6.61 ± 2.13) than in patients with complications as compared (5.90 ± 1.27) in patients without complications.

Conclusion: ACS can be presenting manifestation of DM thus each patient of ACS should be screened for diabetes and glucose intolerance. Patients with DM when compared to nondiabetics have increased morbidity and severity after an ACS.

Keywords: Coronary Artery Disease, Diabetes Mellitus, Stress Hyperglycemia, Coronary Angiography.

INTRODUCTION

Coronary Artery Disease (CAD) has emerged as the single most important cause of death worldwide and as well as in India. In 2013 CAD caused an estimated 7.5 million deaths worldwide accounting for 13.3% of all deaths.[1] Diabetes mellitus (DM) is a major risk factor for CAD and among the most common chronic diseases in the world. According to seventh edition of International Diabetes Federation Diabetes Atlas 2015, worldwide around 415 million people are suffering from DM and nearly half of these are undiagnosed. This number is expected to rise to 640 million in 2040. At the same time, another 318 million people have impaired glucose tolerance and this number expected to increase to 482 million in 2040. Compared to nondiabetics, persons having diabetes have a two to fourfold increased risk of development of and death from CAD.[2] In patients having Acute Coronary Syndrome (ACS), more than one in three may be affected by diabetes and those with diabetes have worse outcomes after ACS.[3-5] Also this graded association of increased risk observed in diabetics in the setting of ACS extends to glucose values in the range way below threshold for diabetes.[6] In addition, diabetes is also associated with increased HF risk in the setting of ACS.[7] The primary aim of the study was to define the relationship between HbA1c levels with mortality, morbidity and severity in patients with ACS in both diabetics as well as patients having impaired glucose tolerance.

MATERIAL AND METHODS

This was an observational prospective study done at tertiary centre from December 2014 to December 2015 after obtaining ethical clearance from the institutional ethical board. 110 consecutive cases of acute coronary syndrome were included in the study based on inclusion exclusion criteria. The inclusion criteria were all patients with acute coronary syndrome presenting within 24 hours. Patients who were K/C of Diabetes Mellitus or Coronary Artery Disease or having co-morbidities like sepsis, hemoglobinopathy or chronic kidney disease were excluded from the study. Informed consent was taken from the study participants before the stat of the study. These patients were subjected to detailed history, examination and baseline investigations. Anthropometric measurements like Body mass index, waist circumference and Waist to Hip ratio were calculated. Patients were evaluated for dyslipidemia and HbA1c was done in all patients by HPLC method. ECG, cardiac echocardiography and cardiac enzymes like CPK-MB were done in all patients and coronary angiography was done in half of patients.

The subjects were divided into three groups – nondiabetic, impaired glucose tolerance and diabetic.

STATISTICAL ANALYSIS

Data was analysed using a computer based statistical analysis programme, SPSS (Statistical Program for Social Sciences) version 22.0. The Chi-square test was used wherever comparisons were needed between the two groups for categorical variables and Student's T test was used for continuous variables. A p value < 0.05 was considered significant.

RESULTS

Out of 110 subjects, 81 were males and 29 females. The mean age was 58.17±9.87. Out of 110 patients, 64 (57.2%) were non-diabetic, 27 (24.5%) were diabetic and 20 (18.2%) had impaired glucose tolerance. 46 patients (41.8% of patients) had

[1]Professor and Head of Department, [2]Resident, [3]Associate Professor, Department of Medicine, Gandhi Medical College, Bhopal, India

Corresponding author: Dr. Kaustubh Mundada, Room No. 78,F Block, Gandhi Medical College Hostel, Hamidia Hospital Campus, Bhopal 462001, India

How to cite this article: T. N. Dubey, Kaustubh Mundada, A Arya. Correlation of HbA1c with mortality and severity in acute coronary syndrome. International Journal of Contemporary Medical Research 2016;3(8):2244-2247.

hypertension. 62 patients out of 110 had increased weight (BMI >23) out of which 21 (77.7% of diabetics) were diabetic, 29 (46% of nondiabetic) were non diabetic and 12 (60% of prediabetic) had impaired glucose tolerance. When BMI was correlated with HbA1c, increased BMI was significantly associated with diabetics compared to nondiabetic (p value 0.005).

Dyslipidemia was present in 50 % of the patients (55 patients). 70% of patients with diabetic had dyslipidemia as compared to 50% of prediabetic and 41% of nondiabetic patients. Dyslipidemia was significantly more prevalent in diabetic patients as compared to nondiabetic (p value 0.001.). Similarly low serum high density lipoprotein (HDL) was present in 43 (i.e. 39%) patients and this was also found to be significantly more low in diabetic patients (17 patients i.e. 62.7%) compared to nondiabetics (19 patients i.e. 30.2%) (p value 0.003).

Out of 110 patients in our study, 27 patients had complications (LVD, shock, HF, Arrhythmia) during the course of hospitalization. Out of these 27, 13 were nondiabetic (20.6% of total nondiabetics), 9 were diabetic (37% of total diabetics) and 5 had impaired glucose tolerance (25%) (Table-1). The most common complications were left ventricular dysfunction and heart failure and this were significantly more present in diabetics compared to nondiabetics (p value 0.009). LVD (EF < 40%) was present in 8 out of 27 diabetic patients (i.e. 29.6%) whereas HF was seen in 7 patients (22.2%). The mean HbA1c level was higher in patients with complications (6.61 ± 2.13 in patients with complications as compared 5.90 ± 1.27 in patients without complications, Table-2) and this was statistically significant (p value 0.038).

Severity of CAD was assessed in 58 patients who underwent CAG. Multivessel disease involvement was seen significantly more in diabetics as compared to nondiabetic. The mean HbA1c was found to be significantly more in patients with multivessel disease compared to those without multivessel disease (6.74 vs. 5.86 p value o.048.)(Figure-1).

Category	All complications		Total
	Present	Absent	
Diabetics	10	17	27
	37.0%	63.0%	100.0%
Impaired glucose tolerance	5	15	20
	25.0%	75.0%	100.0%
Non Diabetics	13	50	63
	20.6%	79.4%	100.0%
Total	28	82	110
	25.5%	74.5%	100.0%

Table-1: Correlation of HbA1c with Complications

All complications	Mean hba1c	Std. Deviation	No of Patients
Present	6.61	2.13	28
Absent	5.90	1.27	82
P=0.038 [The Hba1c level was significantly higher in patients with complications]			

Table-2: Correlation of mean HbA1c with Complications

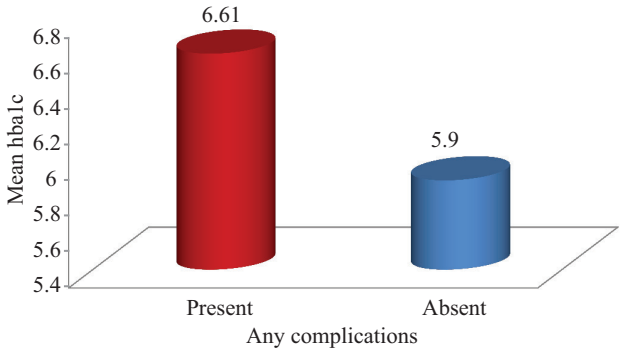

Figure-1: Correlation of HbA1c with complications

DISCUSSION

Though major advances in cardiovascular disease, and specifically the treatment of acute coronary syndrome (ACS), have had a significant impact on the morbidity and mortality of patients with acute myocardial infarctions (AMI), diabetes mellitus (DM) continues to put patients with and without a prior history of myocardial infarction at significant cardiovascular risk.

The presence of DM doubled the age-adjusted risk for cardiovascular disease in men and tripled it in women in the Framingham Heart Study, and it remained an independent risk factor even after adjusting for age, hypertension, smoking, hyperlipidemia, and left ventricular hypertrophy.[8] In a meta-analysis of 13 prospective cohort studies, for every one-percentage point increase in glycosylated hemoglobin (HbA1c), the relative risk for any cardiovascular event was 1.18 (95% CI 1.10–1.26).[9] Also even with all other factors similar, diabetic patients when compared to those without diabetes, have worse long-term outcomes after an acute coronary syndrome.[10,11] Sustained chronic hyperglycemia has been shown to be an important cause for complications and poor outcomes in ACS. Studies have shown that there is a persistent progression of diabetic vascular disease despite reversal of hyperglycemia and this effect of prior hyperglycemia on the initiation and progression of diabetic vascular disease is defined as "metabolic memory".

In our study we found that 27 patients (i.e. 24.5%) with no past history of DM had HbA1c more than 6.4% i.e. they were found to be diabetic. Thus these patients presented to the hospital directly with acute coronary syndrome. Similarly 20 patients (i.e. 18.2%) had HbA1c in the impaired glucose tolerance range (5.7 to 6.4%). Thus patients of DM can have macrovascular complications of diabetes without having the usual symptoms of DM and can directly present with them. This is partly because majority of patients of type 2 DM are asymptomatic and can directly present with chronic complications unlike type 1DM. The classic symptoms of hyperglycemia like polyuria, polydipsia, polyphagia, nocturia, weight loss are often noted only in retrospect when hyperglycemia is noted on laboratory evaluation done either routinely or due to some complication. This findings are similar to other studies like Khaw KT et al[12] which also reported that myocardial infarction may be the initial presentation of diabetes and that there appears to be a graded rise in cardiovascular risk with increasing degrees of glucose intolerance below the definition of overt diabetes. Norhammar A et al[13] reported that previously undiagnosed diabetes and impaired glucose tolerance are common in patients with an acute myocardial infarction. In a meta-analysis of 20 studies that included almost 100,000 people, Coutinho M et al[14] showed that

there was a curvilinear increase in the risk for a cardiovascular event with increasing glucose intolerance. Similarly Haffner AM et al[15] and Juutilainen A et al[16] also showed that diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction.

Increased blood sugar levels performed during the hospitalization in patients could reflect either previously unrecognized diabetes or that the stress of MI unmasks or worsens the tendency toward hyperglycemia. Therefore in our study we used HbA1c levels to categorize patients as diabetic, impaired glucose tolerance and nondiabetics (as per the American Diabetes Association 2003 criteria of HbA1c <5.7% normal; 5.7% to 6.4% impaired glucose tolerance; ≥6.5% diabetes)

In our study we found positive correlation between HbA1c levels and complications. Complications was present in 25% of patients (28 patients) the most common being LVD. Both LVD and HF were more common in diabetics as compared to nondiabetic patients. These findings are in agreement in earlier reports of Mouhamad H et al and Stone P H et al[17] who found that diabetic patients presenting with acute coronary syndrome (ACS) have a worse prognosis. Iribarren C et al[18] in a prospective study of 48,858 adults with DM showed that each 1% increase in HbA1c was associated with an 8% increased relative risk of HF. The clinical manifestations of an acute myocardial infarction are more severe in diabetics than in nondiabetics. Both acute pulmonary edema and heart failure occurs significantly more in diabetics compared to nondiabetics despite similar infarct sizes and left ventricular ejection fractions suggesting that the left ventricle in diabetes tolerates infarction poorly. Diabetic patients have higher LV mass, wall thickness, and arterial stiffness, reduced resting LV ejection fraction (LVEF) and diminished systolic function and reduced cardiac reserve as compared to individuals without diabetes. They also have increased impairment in coronary flow than nondiabetics which might reflect a prothrombotic state or endothelial dysfunction associated with hyperglycemia.

In our study we didn't find any correlation between admission HbA1c levels and outcome.This is in agreement with earlier finding of Corpus RA et al[19], Timmer JR et al[20] and Cakmak M et al[21] who showed that although crude mortality data was higher in patients with elevated HbA1c following adjustment for many cardiovascular risk factors, HbA1c values failed to predict in-hospital mortality. Similarly Hadjadj S, Coisne D et al found no correlation between HbA1c levels and short term outcome of patients. Whereas Chowdhury TA et al[22], Rasoul S et al[23] and Cicek G et al[24] suggested that HbA1c level was also a potent predictor of both in-hospital and long-term mortality. A meta-analysis done by Yao Liu et al found that elevated HbA1c level is an independent risk factor for mortality in CAD patients without diabetes, but not in patients with established diabetes. The negative correlation with outcome in our study may be due to less no of patients and thereby less mortality in our study. It may be also because in our study we followed upand compared mortality of patients for only seven days and didn't compare long term outcome. It may also be due to the fact that in our study we didn't include known diabetic patients but those patients who presented with ACS and then were found to have DM. Another reason might be that short term outcome in ACS is more affected by acute hyperglycemia rather than chronic hyperglycemia of which HbA1c is a marker.

CONCLUSION

As shown in our as well as previous studies, ACS can be the initial presentation of DM and there appears to be a graded rise in cardiovascular risk with increasing degrees of glucose intolerance well below the definition of overt diabetes. Also our study showed that patients with DM when compared to nondiabetics have increased morbidity and severity after an ACS. We conclude that every patient of ACS should be screened for glucose intolerance and diabetes by testing for HbA1c levels and more importantly every person above 35 years of age should be routinely screened for diabetes mellitus and impaired glucose tolerance especially if they have risk factor for insulin resistance like obesity.

REFERENCES

1. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.GBD 2013 Mortality and Causes of Death Collaborators. Lancet. 2015;385:117.
2. Preis SR, Hwang SJ, Coady S, et al.Trends in all cause and cardiovascular disease mortality among woman and men with and without diabetes mellitus in the Framingham heart Study,1950 to 2005.Circulation. 2009;1728:119-123.
3. Fang J, Alderman MH. Impact of increasing burden of diabetes on acute myocardial infarction in New York City;1990-2000. Diabetes. 2012;791:55-57.
4. Gore MO, Patel MJ, Kosiborod M, et al. Diabetes mellitus and trends in hospital survivial after myocardial infarction, 1994 60 2006:data from national registry of Myocardial Infarction. Circ Cardiovasc Qual Outcomes. 2012;791:5-9.
5. Wiviott SD, Braundwald E, Angiolillo DJ, et al.Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel thrombolysis in myocardial infarction 38. Circulation. 2008;1626:118-121.
6. Kosibord M, Inzucchi SE, Krumholz HM, et al. Glucose normalization and outcomes in patients with acute myocardial infarction.Arch Intern Med 169-170;438,2009.
7. Saunders J, Mathewkutty S, Drazner MH, McGuire DK. Cardiomyopathy in type 2 diabetes; Update on pathophysiology mechanism.Herz. 2008;184:33-38.
8. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study.Circulation. 1979;59:8-11.
9. Selvin E, Marinopoulos S, Berkenblit G. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus,‖ Annals of Internal Medicine. 2004;141: 421–431.
10. Haffner SM, Lehto S, Rönnemaa T, PyöräläK, Laakso M;Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction.N Engl J Med. 1998;339:229-132.
11. Mak KH, Topol EJ;Emerging concepts in the management of acute myocardial infarction in patients with diabetes mellitus.J Am Coll Cardiol. 2000;35:563-568.
12. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Association of hemoglobin A1c with cardiovascular

disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med. 2004;141:413-420.
13. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendíc S, Rydén L, Malmberg K; Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet. 2002;359:2140-2148.
14. Coutinho M, Gerstein HC, Wang Y, Yusuf S; The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999;22:233239.
15. Haffner SM, Lehto S, Rönnemaa T, PyöräläK, Laakso M; Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229-233.
16. Juutilainen A, Lehto S, Rönnemaa T, PyöräläK, Laakso M; Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. Diabetes Care. 2005;28:2901-2908.
17. Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB, Turi ZG, Strauss HW, Willerson JT, Robertson T The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. The MILIS Study Group. J Am Coll Cardiol. 1989;14:49-51.
18. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JVGlycemic control and heart failure among adult patients with diabetes. Circulation. 2001;103:2668-72.
19. Corpus RA, O'Neill WW, Dixon SR, Timmis GC, Devlin WH. Relation of hemoglobin A1c to rate of major adverse cardiac events in nondiabetic patients undergoing percutaneous coronary revascularization. Am J Cardiol. 2003;92:1282–86.
20. Timmer JR, Ottervanger JP, Bilo HJ, Dambrink JH, Miedema K, Hoorntje JC et al. Prognostic value of admission glucose and glycosylated haemoglobin levels in acute coronary syndromes. QJM. 2006;99:237–43.
21. Cakmak M, Cakmak N, Cetemen S, Tanriverdi H, Enc Y, Teskin O et al. The value of admission glycosylated hemoglobin level in patients with acute myocardial infarction. Can J Cardiol. 2008;24:375–8.
22. Chowdhury TA, Lasker SS: Elevated glycated haemoglobin in non-diabetic patients is associated with an increased mortality in myocardial infarction. Postgrad Med J. 1998; 74:480-1.
23. Rasoul S, Ottervanger JP, Bilo HJ, Timmer JR, van 't Hof AW, Dambrink JH et al. Glucose dysregulation in nondiabetic patients with ST-elevation myocardial infarction: Acute and chronic glucose dysregulation in STEMI. Neth J Med. 2007;65:95–100.
24. Cicek G, Uyarel H, Ergelen M, Ayhan E, Abanonu GB, Eren M et al. Hemoglobin A1c as a prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. Coronary Artery Disease. 2011;22: 131–37.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 19-06-2016; **Published online**: 21-07-2016